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Publication date:
2010

Document Version
Publisher's PDF, also known as Version of record

Mechanistic study of the ruthenium-catalyzed synthesis of amides from alcohols and amines

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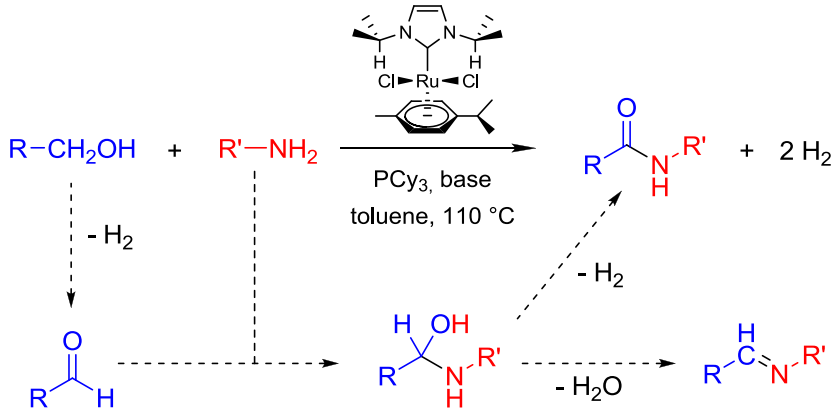
The amide bond is one of the most important linkages in organic chemistry and constitutes the key functional group in peptides, polymers and many pharmaceuticals.[1,2] Amides are often prepared by coupling of carboxylic acids and amines by the use of either a coupling reagent[3] or by prior conversion of the carboxylic acid into a derivative such as the acid chloride. Recently in Madsen group a new method for amide synthesis has been discovered where alcohols and amines are coupled directly with the liberation of hydrogen[5] (Scheme 1).



Scheme 1. ***Amide formation from alcohols and amines.***

The mechanistic studies of this reaction are divided into an experimental part and a theoretical part. In the experimental studies reaction orders for all reactants are determined, para-substituted benzyl alcohols are used as substrates to elucidate the electronic influence of the para substituent, *i.e.* a Hammett study. To gain further insight into the mechanism, a computational study is also carried out. By using DFT calculations with the B3LYP or M06 functionals Gibbs free energies and structures are determined for some metal complexes and transition states in the proposed catalytic cycle. From the experimental and theoretical studies the rate determining step will be established which is important to further optimize the reaction. With an accurate theoretical model, it will be possible to design improved catalyst structures *in silico*, e.g. to determine the optimum *N*-heterocyclic carbene ligand for the reaction.

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